## REMARKS

Introductory Comments

Reconsideration of the above-identified application in view of the above amendments and following arguments is respectfully requested.

Claims 27-38 are pending and under consideration. The specification and claims 27, 31 and 34-36 have been amended as explained below. No new matter has been added as a result of these amendments.

Further, it appears that the Examiner was unaware of the Preliminary Amendment herein dated March 7, 2002. In that Preliminary Amendment, original claims 1-26 were canceled and claims 27-38 were added, but the Office Action refers only to canceled claims 1-26. Enclosed herewith is a copy of this Preliminary Amendment along with the returned postcard receipt. Further, in order to advance prosecution of this application, Applicant has attempted herein to address issues raised by the Office Action to hopefully eliminate such issues from being seen hereafter as applicable to claims 27-38.

Priority

The specification has been amended to recite that this application is a continuation of U.S. Application Serial No. 09/415,796, filed on October 11, 1999, now U.S. Patent No. 6,413,780 which is a non-provisional application of U.S. Application Serial No. 60/104,191, as requested by the Examiner.

General Comments Regarding the Invention

The following explanation is provided in an effort to facilitate the Examiner's understanding of the present invention.

The determination of an item of interest in a biological sample is also known as assaying. In biological assays, the sample is a biological sample that is usually collected from a human or an animal, placed inside a container and is

thereafter analyzed. The details of the analysis depend on the type of information that is desired. The analysis may require the use of reagents and changing the environment for a chemical reaction such as the temperature. Such machines that hold these containers which hold these samples are generally called thermal cyclers.

The method and apparatus according to the present invention pertain to thermal cycling of biological samples such as nucleic acid mixtures using metered amounts of heated or chilled fluids at two or more fixed temperatures. Intermediate temperatures are possible with proportional metering of the fixed temperature fluids. The method according to the present invention allows simple automation of individual thermal profiles of adjacent individual reaction mixtures. Rapid temperature changes are possible in this low-mass system, with the method allowing lockstep operation for a plurality of samples requiring individual or unique cycling conditions.

With conventional thermal cyclers, temperature control occurs in a block or platen in which individual disposables or samples are placed. Blocks are vulnerable to thermal gradients and also become a parasitic thermal mass when the temperature is changed for the next thermal cycle. In contrast, the method according to the present invention has no thermal gradient (from sample to sample) and also is rapid (in changing temperature) because no block is used. Also, random access is possible at an individual sample level.

The following are advantages according to the present invention:

1) allows random access thermal cycling (individual thermal profiles),
2) rapid temperature transitions due to low-mass construction,
3) physically compact design,
4) simple temperature control (no local temperature control, the fluid reservoirs have precise temperature control, the area around the disposable has no control and all of these factors simplify the design),
5) proportional metering allows any intermediate temperature,
6) thin-film design is used which is very inexpensive and also very low waste for disposal, and

7) easily automatable.

Specification Objection

The specification is objected to as not being written in "such full, clear, concise, and exact terms" as to enable any person skilled in the art to practice the invention in its best mode.

The Examiner states that the Summary of the Invention is written in a very confusing and unclear manner such that it does not provide a clear idea of the essence of the invention.

Specifically, the Examiner states that:

1) the definition of the method according to the present invention, "a method of performing a determination of an item of interest in a sample using a single structure" is unclear as to what is being determined and how is it determined,
2) the phrase "a sample is provided accessible to the single structure" is unclear because it is unclear what a "single structure" is and what sample is inaccessible to the structure,
3) it is unclear where the sample is transferred from,
4) it is unclear if there is any connection between adding a reagent to a container and the separation of an "item of interest",
5) the expression "content of the second container is brought to a first temperature different from a temperature of the first process path in the second process path" is unclear,
6) it is unclear how the item of interest in the second container is detected, and
7) it is unclear why the temperature should be different for the item to be detected.

The Examiner suggests defining the determination of the item of interest as detecting an analyte.

Applicants respectfully traverse this rejection.

Regarding point 1) above, Applicants respectfully point out to the Examiner that in the "Background" section which precedes the "Summary" section, the specification states that the item of interest can be "all or portions of a specific region of DNA, RNA, ... peptides, ... enzymes, ... proteins, ... antibodies, ... parts of biological entities such as cells, ... etc." The item of interest is further defined in the specification on page 6, line 19 to page 7, line 7. Applicants submit that one of ordinary skill in the art would understand the invention when reading the entire specification.

However, in an effort to expedite prosecution, Applicants have amended the specification in the Summary section to briefly describe the item of interest and how the item of interest is determined as suggested by the Examiner. Applicants thank the Examiner for her suggestion.

Regarding point 2) above, Applicants submit that the term "accessible" is well-defined as "easy to get to", "nearby", "reachable" or "within reach" in a dictionary or a thesaurus. One skilled in the art would understand, from reading the entire disclosure, that a "single structure" means a single machine although the term "single" is relative. However, upon reviewing the specification, one skilled in the art would understand that this phrase is referring to one machine instead of a large number of machines. Applicants further submit that in determining the best mode of the invention, one skilled in the art may have to read the entire disclosure, not just part of the specification in isolation. It would be improper not even to read the definitions provided in the specification and only focus on part of the specification such as the Summary section. Therefore, Applicants respectfully submit that one skilled in the art would understand from this phrase that a single structure (single machine as opposed to a large number of machines) is used to access a sample easily that is nearby or within reach.

Regarding point 3), Applicants submit that one of ordinary skill in the art, (the assaying art, or the art of determining samples from biological materials), would understand this phrase as meaning sample collection and preparation for analysis. Thus, a technician in the art would place the sample coming from outside a container to inside the container. In order to alleviate the Examiner's

concerns, Applicants have amended the phrase on page 2, lines 12-13 to read "The sample is transferred from outside the first container to inside the first container in the first process path.". Support for this amendment can be found on page 12, lines 11-13.

Regarding point 4), Applicants submit that depending on the type of biological material that is being analyzed (or the type of sample that is assayed), one of ordinary skill in the art would know what reagents are needed, if any, for the particular type of assay.

Regarding points 5) and 7), Applicants submit that the expression, "content of the second container is brought to a first temperature different from a temperature of the first process path in the second process path" is clear to one of ordinary skill in the art. This phrase merely means that there are two different temperatures in each container in each path. One skilled in the art of assays would understand from the specification that different temperatures may be used in a different part of an assay.

Regarding point 6), Applicants submit that exactly how the item is detected depends on the type of biological material in the sample and the type of assay that is used.

Applicants respectfully submit that the level of skill in this area of technology is high and one of ordinary skill in the art would understand the invention.

Accordingly, Applicants respectfully request withdrawal of the objection to the specification for not being written in "such full, clear, concise, and exact terms" as to enable any person skilled in the art to practice the invention in its best mode.

35 U.S.C. § 112, First Paragraph - Enablement

The Office Action has raised concerns (applied to cancelled claims 19-24) under 35 U.S.C. § 112, first paragraph, regarding whether some previously recited inventions were described in the specification in such a way as to enable

one skilled in the art to which it pertains, or which it is most nearly connected, to make and/or use the invention.

Specifically, the Office Action noted a recitation of separating "an item of interest" from the contents of the container, varying the temperature of the content in the container and detecting the "item of interest in the container", while the item is absent from the container since it was separated from the content of the container in the first place, and from this has concluded that no one of ordinary skill in the art can practice such a the claimed method.

Applicants respectfully traverse this rejection and, in any event, have amended the pending claims to address this issue. Specifically, Applicants have amended claim 35 and 36 by deleting "contents" and inserting "the item of interest" therefor. Additionally, claims 27 and 35 have been amended to recite "transferring a sample from outside a container to inside the container" in order to address the specification objection above; claims 27 and 31 have been amended to correct the typographical errors; and claim 34 has been amended to correct the improper claim dependency.

The Office Action also raised a 35 U.S.C. § 112, first paragraph, enablement issue with respect to the specification enabling a method involving separation of the analyte ("item of interest") bound to the solid phase support, including beads, but not supposedly reasonably providing enablement for other methods. As noted in the General Comments regarding the invention above, the invention pertains to thermal cycling. Thermal cycling can be used to hybridize an item of interest with probes or primers in order to determine the item of interest. Moreover, while the specification discloses (page 27, lines 7-26) that capillary tubes, reaction vessels, heat transfer/detection apparatus and the like, can be used in the method according to the present invention, it also discloses (as also noted above) that different items of interest can be determined (pages 1-2 and 6-7). Applicants submit that one skilled in the art would understand from the disclosure how different items of interest can be differently determined through techniques known to the ordinary artisan in combination with the method according to the present invention. Moreover, the advantageous method as

claimed is clearly not limited to determining any particular specific analyte, but instead is more broadly applicable to many different such processes in which two temperatures are desirable as may be advantageously provided according to the claimed method.

For these reasons, Applicants respectfully submit that the pending claims 27-38 all comply with 35 U.S.C. § 112, first paragraph.

35 U.S.C. § 112, Second Paragraph

The Office Action has also raised concerns (applied to canceled claims 1-26) under 35 U.S.C. § 112, second paragraph, regarding whether claims were indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Office Action asserts that the independent claims were difficult to understand as stated above with respect to the Summary section of the specification.

Applicants respectfully submit that such a rejection is not proper as applied to the prior, and particularly the currently pending, claims for the same reasons as set forth previously herein with respect to the Summary section of the specification. Moreover, Applicants have amended the pending independent claims to conform to the Examiner's comments with respect to the now canceled claims.

As to other specific 35 U.S.C. § 112, second paragraph, issues raised in the Office Action:

1) The Office Action questions the phrase "the item of interest" in describing the contents in both the first container and the second container because, according to the Examiner, "the item of interest" may change. Applicants respectfully point out to the Examiner that although part of a sample may change in a detection method, the item of interest will remain the same.
2) The Office Action raises the difference between the term "determining" and "detecting" with respect to the contents of the second container. Applicants submit that an item of interest can be determined if it is

detected. Applicants submit that although the terms are not completely synonymous, their definitions are similar and one skilled in the art would understand the scope of the claims. Moreover, such claim variance is permissible practice to protect against unintended narrow limitation of a patent.

3) The Office Action also questions the phrase "a second first container" based on the understanding that a container can only be either first or second but not both. In this case, however, it must be recognized that the "first container" designates a first group of containers, such as those in a first path, and in this first group of containers there can be a sequential number of containers. Therefore, there can be a first first-container and a second first-container. Applicants submit that this language is acceptable in mechanical claims drafting.
4) The Office Action questions the reason for sealing and then unsealing the containers. Applicants submit that sealing the container can be for preventing contamination, and the sealing can be useful even if it is not throughout the entire assaying process.

The Office Action has questioned *many* different phrases within the canceled claims, some of which are repeated in the present claims. Applicants have attempted to address most of these above and submit that the other claim language is proper according to the English language and acceptable patent prosecution practice. The claims must be interpreted in light of the specification, and based on this it is submitted that one skilled in the art would be able to understand the instant claims.

For all of the above reasons, Applicants respectfully submit that pending claims 27-38 all comply with 35 U.S.C. § 112, second paragraph.

Double Patenting Rejections

Claim 8 was rejected under 35 U.S.C. § 101 as claiming the same invention as that of claim 1 of prior U.S. Patent No. 6,413,780, and claims 1-7 and 9-11 were rejected under the judicially created doctrine of obviousness-type

double patenting as being unpatentable over claims 1-11 of U.S. Patent No. 6,413,780.

As noted above, claims 1-26 were canceled in the Preliminary Amendment dated March 7, 2002. Therefore, it is believed that these rejections are moot.

Rejection of Claims 25-26 Under 35 U.S.C. § 102(b)

Canceled claims 25-26 were rejected under 35 U.S.C. § 102(b), as being anticipated by Hoskins *et al.*, U.S. Patent No. 3,883,305 (herein "Hoskins").

While that rejection is moot (as those claims were canceled in 2002), to advance prosecution of this matter Applicants respectfully submit that Hoskins does not anticipate pending claims 27-38. Hoskins does not disclose or suggest, for example, a process path including a plurality of second process sub-paths.

Accordingly, Applicants respectfully submit that claims 27-38 are allowable under 35 U.S.C. § 102(b) over Hoskins *et al.*, U.S. Patent No. 3,883,305.

Rejection of Claims 1-18 Under 35 U.S.C. § 103(a)

Claims 1-18 were rejected under 35 U.S.C. § 103(a), as being unpatentable over Choperena *et al.*, U.S. Patent No. 5,380,487 (herein "Choperena") in view of the same Hoskins above.

While that rejection is also moot, to advance prosecution Applicants also respectfully submit that claims 27-38 are also patentable under 35 U.S.C. § 103(a) because, *inter alia*, Choperena does not remedy the above noted deficiency of Hoskins.

## CONCLUSION

Applicants respectfully submit that the claims comply with the requirements of 35 U.S.C. Sections 101, 112, 102 and 103. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

Further, given that the Office Action was based on previously canceled claims, it is respectfully submitted that, in the event that the Examiner applies a rejection to the claims which have not yet been considered, any such action should be non-final.

Should the Examiner have any questions concerning the above, he/she is respectfully requested to contact the undersigned at the telephone number listed below. If the Examiner notes any further matters which the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact the undersigned.

Respectfully submitted,

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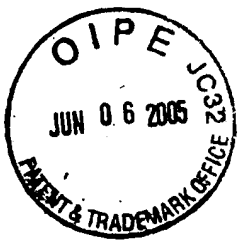
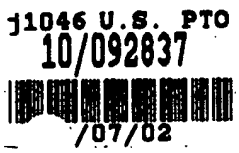



**6416.US.C1** **DJS/ADD/JF** **March 7, 2002**

Patent Office Mail Room: Will you please affix the Patent Office Stamp and return this card to acknowledge receipt of the following documents:

Applicants: M. Bach
Serial No.: Not yet assigned
Filing Date: March 7, 2002
Title: STRUCTURE AND METHOD FOR PERFORMING A DETERMINATION OF AN ITEM OF INTEREST IN A SAMPLE




1. Utility Patent Application Transmittal
2. Fee Transmittal, in duplicate
3. Specification (62 pages, Drawings, 31 pages)
4. Copy of Oath/Declaration (4 pages)
5. Preliminary Amendment (4 pages)
6. Return Receipt Postcard

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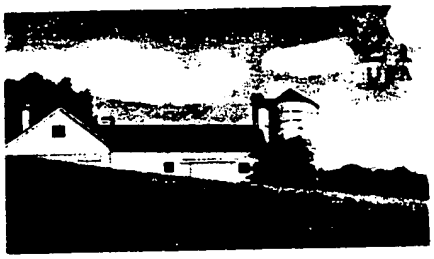

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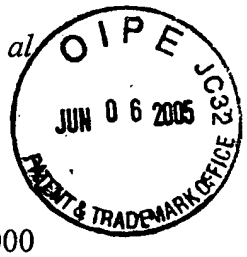


Applicant: Mark C. Bach, *et al*

Docket No.: 6416.US.C1
Anticipated Classification
of this Application:
Class: 436 Subclass: 164000

Prior Application Serial No.: 09/415,796

For: STRUCTURE AND METHOD FOR PERFORMING A DETERMINATION OF AN ITEM OF INTEREST IN A SAMPLE

Examiner: P. Bex

Group Art Unit: 1743

Express Mail Mailing Label Number
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I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being deposited with the United States Postal Service as Express Mail Post Office to Addressee Service under 37 C.F.R. 1.10 on the date shown below with sufficient postage addressed to the:

Assistant Commissioner for Patents
Box: Patent Application
Washington, D.C. 20231, on:

Date of Deposit: MARCH 7, 2002

Julie Freeman 3/7/02
Date

Assistant Commissioner for Patents
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Washington, D.C. 20231

**PRELIMINARY AMENDMENT**

Dear Sir:

The following amendment accompanies the 37 C.F.R. 1.53(b) Continuation Application of U.S. Serial No. 09/415,796. Examination of this continuation application, based upon the following amendment, is requested.

## AMENDMENTS

In the claims:

Please cancel claims 1-26, and substitute therefor:

27. A method of performing a determination of an item of interest in a sample using a single structure, the single structure having a first process path and a second path, and the second process path including a plurality of second process sub-paths, the method comprising the steps of:

(a) transferring a sample to a first container in a first process path on the single structure;

(b) separating an item of interest in the sample from the contents of the first container in the first process path;

(c) transferring the separated item of interest in the sample from the first container in the first process path to a second container in at least one of the plurality of second process sub-paths of the second process path on the single structure;

(d) bringing contents of the second container to a first temperature different from a temperature of the first process path in the second process path; and

(d) detecting the item of interest in the second container in the second process path.

28. The method of claim 27 further comprising the step of:

(f) sealing at least one of the first container and the second container.

29. The method of claim 28 further comprising the step of:

(g) removing the seal from at least one of the first container and the second container.

30. The method of claim 27 further comprising the step of:

(f) reducing exposure of contents of at least one of the first container and the second container to a contaminant.

31. The method of claim 27 further comprising the step of:

(f) bringing contents of the second container to a second temperature different from the first temperature in the second process path.

32. The method of claim 27 further comprising the steps of:

(f) transferring a second sample to a second first container in the first process path;

(g) adding a reagent to the second first container in the first process path;

(h) transferring contents of the second first container to an optical flow cell on the single structure;

(i) illuminating the optical flow cell; and

(j) detecting the item of interest in the sample in the optical flow cell.

33. The method of claim 27 wherein the sample is maintained at more than one temperature in the first process path.

34. The method of claim 29 wherein the first process path includes more than one temperature controller.

35. A method of performing a determination of an item of interest in a sample using a single structure, the method comprising the steps of:

(a) transferring a sample to a container in a process path on the single structure, wherein the process path includes a plurality of sub-paths;

(b) separating an item of interest in the sample from the contents of the container in the process path;

(c) bringing contents of the container to a first temperature in the process path;

(d) transferring the container to at least one of the plurality of sub-paths;

(e) bringing contents of the container to a second temperature different from the first temperature in the process path; and

(f) detecting the item of interest in the container in the process path.

36. The method of claim 35 further comprising the step of:

(g) reducing exposure of contents of the container to a contaminant.

37. The method of claim 35 wherein a determination of an item of interest comprises the steps of:

(g) discerning determinations to be performed by the single structure;

(h) sorting samples provided to the single structure by at least one common process; and

(i) transferring the samples to the first process path in an order determined by sorting step (h).

38. The method of claim 37 further comprising the step of:

(i) allocating an element of the single structure to a given determination based on sorting step (h).

REMARKS

This is a continuation application of co-pending application No. 09/415,796. Pending claims 27-38 correspond to those claims canceled without prejudice by way of the Examiner's Amendment dated December 14, 2001 in the parent application. Thus, no new matter has been added by way of the present amendment. If, in the opinion of the Examiner, a telephonic interview would desirably advance the prosecution of the present application, the Examiner is invited to contact applicants' undersigned representative.

Respectfully submitted,

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